REMARKS

The Office Action of May 5, 2003 has been reviewed and the Examiner's comments carefully considered. Claims 7 and 12-15 are currently pending in this application. Claim 15 is canceled and claim 7 is amended. Support for the language in claim 7 is found in Example 5 of the specification, by converting the dosage amount of 50 to 200 μg/kg body weight of human plasmin administered to animals weighing approximately 30 grams to a comparable effective dosage amount for human administration. No new matter has been added.

The specification is objected to because it does not contain a section entitled "Brief Description of the Drawings." The Examiner is directed to the Preliminary Amendment, filed March 28, 2001, in which the specification was amended to include the above-described section.

Claim 15 stands rejected under 35 U.S.C. 112, first paragraph, for asserted lack of a written description. Claim 15 has been canceled, which moots this rejection. Claims 7 and 12-14 stand rejected under 35 U.S.C. 112, first paragraph, for asserted lack of enablement, and to support this assertion, the Examiner cites four references to illustrate the state of the art of plasmin, plasmin mutants, and hybrids. Two of the references were published after the priority date of the present invention: Nagai et al., published in 2001, and Lapchak et al., published in 2002. Applicants therefore rebut this rejection by pointing out that, according to *In re Hogan*, 194 USPQ 527 (CCPA 1977), articles published after the priority date of an application may not properly be used as evidence of an unpredictable state of the art as of the time of filing. *In re Hogan,* therefore, stands for the constraint that enablement must be considered as of the filing date and not as of a later date. The other two references cited by the Examiner, Reddy (1998) and Bell (1997), are cited by the Examiner in order to assert that the present invention lacks predictability in the art and would require undue experimentation, even though the Examiner states that the Reddy reference discloses the ease with which such mutations can be made. Applicants rebut this enablement rejection by referring the Examiner to the attached expert's Declaration, in which the Declarant attests that the production of proteins or polypeptides having the active catalytic site of plasmin, such as miniplasmin and microplasmin, is a well-known technology in the art that has been

available for several decades and thus would not require undue experimentation by those skilled in the art (Paragraph 9). For example, the production of miniplasmin, a plasmin lacking kringles 1-3 and thus composed of kringle 4 and 5, but having the active catalytic site of plasmin, has been available as early as 1995. *Christensen et al., Biochem. J. (1995) 305 (Pt 1): 97-102.* Indeed, the generation of miniplasmin composed of kringle 5 and having the active catalytic site of plasmin has been known since 1979. *Christensen et al., Biochim. Biophys. Acta (1979) 567: 472-481.* The Declarant further attests that it is well-known that elastase digestion of plasmin yields two fragments: miniplasmin and angiostatin (Paragraph 9).

Thus, the development of compounds having the catalytically active site of human plasmin is a well-known technology that would require no undue experimentation by those skilled in the art. Finally, all treatments employing thrombolytic compounds inherently contain a certain degree of risk for bleeding, and the associated risks are well-known but better than death as an alternative.

Claims 7 and 12-14 stand rejected under 35 U.S.C. 102(b) as assertedly anticipated by Eibl et al. The Examiner asserts that, although Eibl does not disclose that the plasmin in its patent is specifically responsible for neutralizing α_2-antiplasmin activity, it is still acting in the manner claimed by the present invention because "a product inherently possesses the properties of the product." Applicants rebut this rejection by directing the Examiner to Paragraph 10 of the expert's Declaration, in which it is stated that the lys-plasminogen pharmaceutical composition disclosed by Eibl does not and cannot inherently possess the properties of the plasmin, miniplasmin, microplasmin, and mutants and hybrids thereof because plasminogen activation occurs only <u>locally</u> at the site of a clot, with only trace amounts of plasmin generated even locally. Thus, the systemic administration of plasminogen or its derivatives, such as lys-plasminogen, taught by Eibl et al., does not and cannot generate circulating levels of plasmin high enough to react stoichiometrically with α_2-AP to effect its neutralization. Plasminogen and its derivatives, therefore, have no inherent capability of binding to circulating α_2-AP because the conversion of plasminogen to plasmin occurs only locally at the site of the clot or infarct (the extrasystemic compartment), and not

systemically (the systemic compartment). As stated by the Declarant, spatial segregation of endogenous moieties in an organism is known as compartmentalization, a concept that makes any inherency argument with regard to plasminogen activation leading to circulating levels of plasmin impossible, because such activation, if it happens at all, occurs only locally and not systemically.

In particular, plasminogen is an inactive plasma protein that is converted to the active protein plasmin, locally, i.e., at the site of a clot, or infarct. It is plasmin, a proteolytic enzyme, that is responsible for clot lysis by digesting fibrin and destroying many other clotting factors. That is to say, when a clot is formed, a large amount of plasminogen from the circulation is absorbed into the clot, but clot lysis will not occur until plasminogen is activated into plasmin by a plasminogen activator, such as tissue plasminogen activator, compounds present only at the site of the clot and not found in the circulation. Plasminogen activation thus occurs locally at the site of the clot, and only trace amounts of plasmin are generated at the local site of the clot or infarct. Plasmin therefore is not found in the circulation (the systemic compartment) but only locally (the extrasystemic compartment). Thus, endogenous (naturally occurring) plasminogen or administration of exogenous plasminogen, or derivatives thereof (such as the lys-plasminogen disclosed by Eibl et al.) does not and cannot generate circulating levels of plasmin. The Applicants submit, therefore, that it is a physiochemical impossibility for the pharmaceutical composition disclosed by Eibl et al., i.e, lys-plasminogen and plasmin inherently to possess the properties of circulating plasmin because administration of this pharmaceutical composition does not generate circulating levels of plasmin.

The Declarant attests that systemic administration of plasmin, microplasmin or miniplasmin in a dosage amount ranging between 1.5 to 7.0 mg/kg body weight will effectively neutralize 100% of circulating α_2-AP, resulting in significant reduction in the size of cerebral ischemic infarcts (Paragraph 8). These dosage amounts are not taught by the Eibl et al. reference because Eibl et al. disclose only dosage amounts for lys-plasminogen and neither address nor suggest what plasmin dosages need to be systemically administered for any purpose. Moreover, even if one could convert the dosage amounts for lys-plasminogen to a comparable plasmin dosage, because lys-plasminogen activation occurs only locally at

the site of the infarct *in vivo* and produces only trace amounts of plasmin thereon, as described above, any conversion amount calculated from such a conversion would be irrelevant for determining the dosage amount of circulating plasmin needed to neutralize circulating α_2-AP.

For all the foregoing reasons, amended claim 7 and therefore claims 12-14, which depend from claim 7, are patentable over the cited prior art and in condition for allowance. Withdrawal of the asserted rejections and allowance of all pending claims 7 and 12-14 is respectfully requested.

Respectfully submitted,

WEBB ZIESENHEIM LOGSDON
ORKIN & HANSON, P.C.

By _____

Barbara E. Johnson
Registration No. 31,198
Attorney for Applicants
700 Koppers Building
436 Seventh Avenue
Pittsburgh, PA 15219-1818
Telephone: 412-471-8815
Facsimile: 412-471-4094